PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/00, 31/415, 31/05, 31/557, 31/38 | A1

(11) International Publication Number: WO 96/40090

(43) International Publication Date: 19 December 1996 (19.12.96)

(21) International Application Number: PCT/US96/08216

(22) International Filing Date: 31 May 1996 (31.05.96)

(30) Priority Data:
08/473,183 7 June 1995 (07.06.95) US

(71) Applicant: UNIVERSITY OF SOUTHERN CALIFORNIA [US/US]; University Park Campus, Los Angeles, CA 90089 (US).

(72) Inventors: RODGERS, Kathleen, Elizabeth; 4403 Galeano Street, Long Beach, CA 90815 (US). diZEREGA, Gere, Stodder; 1270 Hillcrest Avenue, Pasadena, CA 91105 (US).

(74) Agent: MIAO, Emily; Banner & Allegretti, Ltd., Ten South Wacker Drive, Chicago, IL 60606 (US).

(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHOD FOR REDUCING OR PREVENTING POST-SURGICAL ADHESION FORMATION USING 5-LIPOXYGENASE INHIBITORS

(57) Abstract

Compositions and methods for minimizing or preventing post-surgical adhesion formation between tissues, e.g., organ, surfaces in body cavities, whereby an effective therapeutic amount of at least one 5-lipoxygenase inhibitor, e.g., phenidone, NDGA, ETYA and Zileuton, is administered to the target injury site for a period of time sufficient to permit tissue repair. The 5-lipoxygenase inhibitor is preferably administered in conjunction with a delivery vehicle (e.g., microcapsules, microspheres, biodegradable polymer films, lipid-based delivery systems such as liposomes and lipid foams, crystalloid or viscous instillates and absorbable mechanical barriers) useful for maintaining local concentrations of the inhibitor at the injury site at an effective level for a sustained period of time.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

METHOD FOR REDUCING OR PREVENTING POST-SURGICAL ADHESION FORMATION USING 5-LIPOXYGENASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to 5-lipoxygenase (5-LO) inhibitors and their use thereof in a method for reducing or preventing post-operative adhesion formation between tissue, e.g., organ, surfaces in a body cavity.

BACKGROUND OF THE INVENTION

Adhesion formation, in particular following peritoneal surgery, is a major source of postoperative morbidity and mortality. Appendectomy and gynecologic surgery are the most frequent surgical procedures implicated in clinically significant adhesion formation. The most serious complication of intraperitoneal adhesions is intestinal obstruction; in addition, adhesions are associated with chronic or recurrent pelvic pain and infertility in females.

The pathogenesis of adhesion formation is complex and not entirely understood. The first step is believed to involve excess fibrin deposition to form a scaffold. Organization of the fibrin scaffold by cellular elements, including fibroblasts and mesothelial cells, then follows.

Various approaches for the prevention of adhesion formation have been actively explored [diZerega, G.S. & Rodgers, K.E., "Prevention of Postoperative Adhesions," in "The Peritoneum," diZerega, G.S. & Rodgers, K.E., eds., Springer-Verlag, New York, pp. 307-369 (1992)]. In general, the treatments fall into three categories: prevention of fibrin deposition in the peritoneal exudate, reduction of local tissue inflammation; and removal of fibrin deposits.

Therapeutic attempts to prevent fibrin deposition include peritoneal lavages to dilute or wash away fibrinous exudate, surgical techniques to minimize tissue ischemia and introduction of barriers to limit apposition of healing serosal surfaces. Although the use of agents affecting coagulation of the fibrinous fluid has also been proposed, results obtained to date suggest that the use of procoagulants in areas of substantial bleeding may actually promote adhesion formation [Elkins, T.E., "Can a Pro-Coagulant Substance Prevent Adhesions?" in "Treatment of Post-Surgical Adhesions," diZerega, G.S. et al., eds., Wiley-Liss, New York, pp. 103-112 (1990)].

Physical barriers have been used in attempts to prevent adhesion formation by limiting tissue apposition during the critical period of peritoneal healing, thereby minimizing the development of fibrin matrix between tissue surfaces. Barrier agents which have been employed include both mechanical barriers and viscous solutions. Mixed results have been obtained using a barrier comprising a thin sheet of expanded poly-tetrafluoroethylene; in any event, such a membrane is less than ideal, as it must be sutured into place and is nonabsorbable. While an absorbable barrier (for example, a barrier made of oxidized regenerated cellulose) would be preferable, not all studies have demonstrated the efficacy of such barriers in preventing adhesions. Liquid barriers have also been considered for use in preventing adhesions; for example, chondroitin sulfate and carboxymethyl cellulose have both shown some promise in animal models. In addition, solution of dextran 70 (molecular weight = 70,000) has been the subject of a number of clinical studies. Not all clinical evaluations of 32% dextran 70 have found a therapeutic effect, however, and the clinical use of the solution is also associated with clinically important side effects.

Anti-inflammatory drugs have been evaluated for their effects on postoperative adhesion formation, as they may limit the release of fibrinous exudate in response to inflammation at the surgical site. Two general classes of these drugs were tested: cortico-steroids and nonsteroidal anti-inflammatory drugs. The results of corticosteroid use in animal studies have generally not been encouraging, and clinical use of corticosteroids is limited by their other pharmacologic properties. While experimental evaluations of nonsteroidal anti-inflammatory drugs in postoperative adhesion formation show promise [Rodgers, K.E., "Nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of Postsurgical adhesion," in "Treatment of Post-Surgical Adhesions," diZerega, G.S. et al., eds., Wiley-Liss, New York, pp. 119-129 (1990)], clinical evaluations of these drugs for adhesion prevention is needed.

The third approach explored to date involves the removal of fibrin deposits. Although proteolytic enzymes (e.g., pepsin, trypsin and papain) should theoretically augment the local fibrinolytic system and limit adhesion formation, these enzymes are rapidly neutralized by peritoneal exudates rendering them virtually useless for adhesion prophylaxis. While various fibrinolytics (for example, fibrinolysin, streptokinase and urokinase) have been advocated, a potential complication to the clinical use of these enzymes in postoperative therapy is excessive bleeding resulting from their administration. Topical application of a recombinant tissue plasminogen activator (rt-PA) has been shown to reduce adhesion formation in a variety of animal models; further research is necessary to develop suitable delivery systems to provide this drug to the surgical site and identify the postoperative time when adhesion prevention is feasible.

To date, no single therapeutic approach has proven universally effective in preventing formation of postoperative intraperitoneal adhesions. Therefore, there is a need for compositions and methods which may be used safely and effectively to prevent adhesion formation in a variety of different contexts.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide 5-lipoxygenase (5-LO) inhibitor-based compositions for use in preventing or minimizing adhesion formation.

It is another object of the invention to provide a method for reducing or preventing post-surgical adhesion formation between tissue surfaces in body cavities which employ 5-LO inhibitors.

These and other objects of the invention will be apparent in light of the detailed description below.

SUMMARY OF THE INVENTION

The present invention relates to 5-lipoxygenase (5-LO) inhibitors and their use in a method for reducing or preventing adhesion formation between tissue, e.g., organ, surfaces in body cavities comprising administering to a subject an effective amount of at least one 5-LO inhibitor, e.g., phenidone, nordihydroguaiaretic acid (NDGA), 5,8,11,14-eicosatetraynoic acid (EYTA) and Zileuton. The 5-LO inhibitor is preferably administered in conjunction with a drug delivery system which maintains an effective concentration of the compound at a site of potential adhesion formation during the perioperative interval.

Pursuant to another aspect of the present invention, adhesion formation is minimized or prevented by administration of at least one 5-LO inhibitor at a site of potential adhesion formation for a period of time sufficient to permit substantial tissue repair (e.g.,

re-epithelialization or mesothelial repair) at the site.

DETAILED DESCRIPTION OF THE INVENTION

All literature references, patents and patent applications cited in this application are incorporated herein in their entirety.

The inventive composition and method are useful in minimizing or preventing formation of adhesions between organ surfaces (not cell-to-cell adhesion), the most common cause of which is prior surgery. The inventive composition and method have been shown to be especially effective in preventing adhesion formation in the peritoneum following surgery. In addition, the present invention finds utility in other contexts, e.g., for cardiovascular, orthopedic, thoracic, ophthalmic, CNS and other uses, where prevention of the formation of adhesions is a significant concern. For example, prevention of adhesion formation or drug loculation during the intraperitoneal administration of chemotherapeutic agent is contemplated as within the scope of the present invention. For the purposes of the following discussion, attention is directed primarily to description of compositions and methods useful in inhibiting peritoneal adhesion formation.

The present invention is based on the discovery that compounds which inhibit 5-lipoxygenase (5-LO) activity are useful in reducing or preventing formation of adhesions between tissue surfaces in body cavities following surgical procedures. The 5-LO enzyme, found primarily in polymorphonuclear leukocytes (PMNs) and eosinopils, is a major enzyme involved in second pathway (the "5-LO pathway") of arachidonate metabolism in which arachidonic acid is converted to pro-inflammatory products called leukotrienes (LTs). 5-LO catalyses the stereospecific oxidation of arachidonic acid to a 5-hydroperoxyeicosa-tetraenoic acid (5-HPETE) in the initial step towards the

biosynthesis of leukotrienes. The enzyme contains non-heme iron in the active site, and the mechanism of the transformation probably involves an organoiron intermediate or a dienyl radical which is trapped by molecular oxygen. For a review of the properties and proposed mechanisms of 5-LO, see Musser and Kreft (1992), "5-Lipoxygenase: Properties, pharmacology and the quinolinyl (bridged)aryl class of inhibitors", J. Med. Chem., Vol. 35, pp. 2501-2524; Batt (1992), "5-Lipoxygenase inhibitors and their anti-inflammatory activities," Prog. Med. Chem., Vol. 29, pp. 1-63.

Because leukotrienes and other pro-inflammatory arachidonic acid metabolites have been implicated in many inflammatory disease processes such as asthma, rheumatoid arthritis, inflammatory bowel disease, psoriasis and glomerulonephritis, compounds which inhibit 5-LO activity are highly desirable as therapeutic agents. For a review of the role of 5-LO in inflammatory processes, see for instance, Batt (1992), "5-Lipoxygenase inhibitors and their anti-inflammatory activities," Prog. Med. Chem., Vol. 29, pp. 1-63. Prior to the present invention, however, use of 5-LO inhibitors in preventing post-surgical adhesions was unknown.

Numerous compounds of vast structural diversity have been shown to inhibit 5-LO activity. Classes of 5-LO inhibitors based on structure include substrate or product analogs, catechols, phenols, aminophenols, flavinoids, naphthols, heterocycles such quinones, indazolines, and benzothiophenes, and hydroxamic acid derivatives of common NSAIDs. Examples of these classes of compounds are described in the literature, for instance, in Musser and Kreft (1992), "5-Lipoxygenase: Properties, pharmacology and the quinolinyl (bridged)aryl class of inhibitors", J. Med. Chem., Vol. 35, pp. 2501-2524; Salmon et al. (1990), "Inhibition of 5-lipoxygenase: development of hydroxamic

acids and hydroxyureas as potential therapeutic agents," Adv. Prost., Thromb., Leukotriene Res., Vol. 21, pp. 109-112; Riendeau et al. (1989), "Sensitivity of immunoaffinity-purified porcine 5-lipoxygenase to inhibitors and activating lipid hydroxyperoxides," Biochem. Pharmacol., Vol. 38, pp. 2313-2321; Hlasta et al. (1991), "5-Lipoxygenase inhibitors: the synthesis and structure activity relationships of a series of 1-phenyl-3-pyrazolidinones," J. Med. Chem., Vol. 34, pp. 1560-1570. Compounds which inhibit 5-LO activity assert their effect through a variety of mechanisms which include alterations in cellular metabolism, a direct effect on the enzyme leading to reduced function or through competitive inhibition. A recent extensive review describes the representative structural classes of 5-LO inhibitors. See Batt (1992), "5-Lipoxygenase inhibitors and their anti-inflammatory activities," Prog. Med. Chem., Vol. 29, pp. 1-63.

5-LO enzyme is inhibited by substrate and product analogues. Acetylenic, methylated, cyclized, or thia-analogues of arachidonic acid, and cyclopropyl analogues of LTB4 inhibit 5-LO. One compound described further below, 5,8,11,14-eicosatetraynoic acid (ETYA), is a competitive inhibitor of CO and LO. Anderson et al. (1992) "EYTA, a pleotrophic membrane-active arachidonic acid analogue affects multiple signal transduction pathways in cultured transformed mammalian cells," Clin. Biochem., Vol. 25, pp. 1-9. See Batt at 6-7.

Catechols and aminophenols have also been shown to inhibit 5-LO enzyme. Lipophilic catechols, notably nordihydroguaiaretic acid (NDGA) which is used as an example below, were more potent than pyrocatechol. The inactivation of 5-LO enzyme is irreversible, and is accompanied by oxidation of phenolic compound. The ortho-dihydroxyphenyl moiety is required for the best potency

which correlated with overall lipophilicity of the inhibitor. NDGA and other phenolic compounds have been shown by electron paramagnetic resonance spectroscopy to reduce the active-site iron from Fe-(III) to Fe-(II). Electron-poor, less easily oxidized catechols form stable complexes with the active-site iron atom. See Batt at 8-11 and references cited therein.

A large number of catechol-containing compounds have been reported to inhibit a variety of 5-LOs. Many of these are natural products or synthetic analogues, such as gossypol, caffeic acid and derivatives, and a wide variety of other ortho-dihydroxyphenyl compounds. In general, most inhibitors of 5-LO are somewhat less potent against 12-LO, and are often significantly less potent as inhibitors of CO. Potency is often roughly correlated with lipophilicity. Many reports have appeared over the last decade dealing with 5-LO inhibition by flavinoids. The most studied compound is quercetin, α-Tocopherol (vitamin E) represents another class of phenolic lipophilic antioxidants, para-substituted by an oxygen atom in a fused saturated ring which inhibits platelet 12-LO and soybean 15-LO. A series of related benzoxanthiols potently inhibit 5-LO; replacement of the propyl group by ethyl, butyl or phenyl maintains this potency. L-651,896 is a compound from a series of dihydrobenzofuranols. Ibid.

The structure activity relationship (SAR) for L-651,896 and analogues was examined. There is shape specificity for 5-LO inhibition demonstrated by the greater potency of 6-substituted analogues compared to 4-substituted compound. RS-43179 (lonapalene) is a selective 5-LO inhibitor with topical anti-inflammatory activity. SAR studies showed that lipophilicity plays a strong role, but if the compounds are too lipophilic (such as with larger alkoxy groups) activity is reduced. The best substituent on the fused ring is chloro, although other

groups capable of π-electron donation (other halogens, methoxy) are also effective. Hydrolysis of at least one of the ester groups appears essential for activity, since compounds with increasing hydrolytic stability (pivalate, benzoate) are less potent. A similar naphthol derivative from UpJohn is U-66,858 (bunaprolast). Simple 2-substituted 1-naphthols (DuP 654) are both potent 5-LO inhibitors and topical anti-inflammatories. SAR studies showed that various positional isomers are significantly less potent against 5-LO than DuP 654, although the CO inhibition is less sensitive to these changes. Lipophilic phenols lacking the fused ring system, such as 2,6 dibenzylphenol, are also less potent. Lipophilic arylmethyl 2-substituents are favored in vivo although even 2 methyl-1 naphthol is selective (but less potent) for 5-LO. Substitution at the 4-position by electron withdrawing groups reduces potency, as expected for a compound acting by redox mechanism. See Batt at 15-19 and references cited therein.

Heterocyclic naphthol isosteres are also potent 5-LO inhibitors. Heterocyclic analogues of bunaprolast are about equipotent with the isocyclic versions. The hydroxyquinoline N-oxide KF 8940 is a potent inhibitor of 5-LO and is quite selective with respect to inhibition of 12-LO and CO. Another heterocyclic inhibitor (L-656,224) is selective for 5-LO. Like some of the naphthol series, and alkyl substituent (preferable methyl, ethyl or propyl) ortho to the hydroxyl is required for activity; the τ-butyl analogue is less potent, as are analogues with heteroatom-containing chains at the position. Substitution on the benzyl group is relatively unimportant, as long as a carboxyl group is not present. Closely related benzimidazoles shows similar activity. Ibid.

Phenolic compounds, particularly those with para-oxygen substituents, are readily oxidized to quinones.

Likewise, quinones are easily reduced (chemically and metabolically) to 5-LO-inhibiting hydroquinones. AA861 (docebenone) is one such compound which is a standard 5-LO inhibitors used in various physiological and pharmacological studies. The side-chain of docebenone is required for in vitro activity, but partial or full saturation of this group has little effect. Replacement of the methyl groups on the benzoquinone moiety by methoxyls also give similar activity. See Batt at 19-21 and references cited therein.

Amino-substituted naphthoquinones and heterocyclic variants (which are fully conjugated, but non-aromatic) are 5-LO inhibitors. Ibid.

Heterocycles which are fully conjugated, but non-aromatic, such as phenothiazine, are easily oxidized. This redox activity, coupled with the lipophilicity and π-electron character (which is felt to mimic the arachidonic acid chain), led to the development of a series of substituted phenothiazinones such as L-651,392, as selective 5-LO inhibitors. See Batt at 21-23 and references cited therein.

Phenoxazine is a potent inhibitor of 5-LO. Substitution at the 1-position by carboxylic acid, ester or hydroxamic acid decreases potency. Lipophilic substitution at the 2-position is less destructive. A series of substituted dihydrothiazines has also been reported. Substitution on the phenyl group or variation of the benzyl by alkyl or hydroxyalkyl reduces potency about 10-fold. Replacement of the phenyl substituent by benzoyl reduces potency, while reduction of the trisubstituted double bond completely destroys activity. Ibid.

Phenidone and BW-755c are inhibitors of 5-LO. Derivatives of phenidone have been reported; C-alkylation with lipophilic groups alpha to the carbonyl is acceptable, while N-methylation destroys in vitro activity. A

quantitative SAR study of the phenyl ring of BW-755c with respect to activity shows that electron-donating substituents are better than electron-withdrawing ones, and that large substituents are disfavoured, especially in the ortho position. A-53612 is a ring-expanded version of phenidone which is selective for 5-LO. A-65620, a perhydro analogue, is very similar to A-53612, having equal or slightly reduced potency. The pyridazinones are generally more potent than the triazinones; enhanced lipophilicity (by substitution on the 1-phenyl or the heterocyclic ring) increased potency. Acyclic analogues of phenidone, such pyrazolecarboxylic hydrazides, inhibits 15-LO and are inactive against CO. A series of indazolinones, such as ICI 207968, are benzo-fused analogues of phenidone. Some analogues inhibited CO as well, but ICI 207968 itself is highly selective (ca.300-fold) for 5-LO. See Batt at 23-27 and references cited therein.

SAR studies indicate that unsubstituted indazolines inhibit 5-LO, but without selectivity. Substitution on the 1-nitrogen has no effect, while substitution on oxygen or both nitrogens destroys activity. Phenyl and methyl groups replacing the pyridylmethyl of ICI 207968 gives greater potency, but poorer selectivity. Benzyl and heterobenzyl groups give the best profile; lengthening the link group beyond one methylene has little effect. The 1-naphthylmethyl analogue is potent and selective, while the 2-naphthyl analogue has increased CO activity. The 1 naphthylethyl analogue showed good stereoselective action in that the (R) enantiomer was very selective for 5-LO over CO. Other compounds containing heteroatom-heteroatom bonds have been reported as 5-LO inhibitors such as diphenyldisulphides and substituted analogues, as well as disulphiram. Ibid.

N-Hydroxyarachidonamides are potent reversible inhibitors of 5-LO. Alkylation on nitrogen increased the

inhibitory potency significantly. Placement of the hydroxamic acid moiety in 5-position gives analogues of 5-HPETE which also inhibit 5-LO. A series of aralkylhydroxamic acids, represented by 9-phenylnonanohydroxamic acid (BMY 30094), inhibits 5-LO. Small substituents on the phenyl ring (methyl, methoxy, chloro) has little effect on potency, but larger substituents (butyloxy) lead to greatly decreased activity. See Batt at 27-28 and references cited therein.

Hydroxamic acid derivatives of common NSAIDs (meclofenamic acid, indomethacin, sulindac, and ibuprofen) inhibit 5-LO with the following potency: CON(Me)OH>CONHON>CONH(OMe)->COOH. The CO potency ranking is exactly opposite, although the best 5-LO inhibitors still possess significant CO activity. Hydroxamic acids, including many simple ω-aralkylhydroxamic acids, have been extensively studied and yielded potent 5-LO inhibitors. The inhibitory activity correlates most strongly with the over-all lipophilicity. However, hydrophobicity in the immediate vicinity of the hydroxamic acid, as well as greater than 12 angstroms away from this moiety, does not greatly influence potency. The hydroxamic acids have a large lipophilic group attached to the carbonyl, and a small alkyl group on nitrogen. SARs are similar to those observed for the arylacetohydroxamic acids: methyl is favored on the carbonyl group, the best group linking the aryl moiety to the nitrogen was CH(Me), and lipophilic substituents on the phenyl ring, preferably in the para position, are optimal. Heterocycles such as benzothiophene, benzofuran, N-methylindole, and dibenzofuran could also serve as the aryl group. See Batt at 27-32 and references cited therein.

The benzothiophene analogue A64077 (zileuton) is one of the most interesting 5-LO inhibitors studied to date. Although the original rationale for 5-LO inhibition by

hydroxaminacids was iron chelation, this functional group also contains an N-O single bond which is capable of oxidation. N-Alkylhydroxylamines are mixed CO/5-LO inhibitors (approximately equipotent). O-Methylation increases CO potency and decreases 5-LO potency, while N-methylation has the opposite effect, and larger N-substituents decreases activity. Analogues with 7-substituted 2-naphthyl moieties, exemplified by QA 208-199, give the best 5-LO potency. See Batt at 32-33 and references cited therein.

15-HETE inhibits 5-LO. A series of combined 5-LO inhibitors/LT antagonists were derived from the structure of 15-HETE. REV 5901A is the best of the series with respect to CO and 12-LO inhibition. The quinoline could be replaced by another lipophilic aromatic group, but potency is decreased (naphthalene is 40-fold less potent, and substituted phenyl is 5-to-20-fold less active). Pyridines are active but also less potent; 2-pyridyl is only 4-fold less active, while 3- and 4-pyridyl are 20-fold weaker. Ortho- and para- substituted phenylene groups are less active. See Batt at 33 and references cited therein.

Similar naphthalenemethyloxyphenyl compounds are potent, selective 5-LO inhibitors which display no antioxidant or iron chelation properties. Replacement of the ethyl group by hydrogen or methyl decreases activity, as does conversion of the methoxy to the hydroxy. Diaryl 2,3-dihydromidazo [2,1-b]thiazoles in which one of the aryl groups is pyridyl, such as SK&F 86002, are dual CO/5-LO inhibitors. A related series of diaryl pyrrolo [1,2-a]imidazoles, represented by SK&F 104351, 104493 and 105809, show similar profiles. Tepoxaline (RWJ 20485) is a hydroxamic acid derivative which inhibits 5-LO. See Batt at 35 and references cited therein.

As discussed above, a wide variety of agents have been reported as 5-LO inhibitors. The majority of the series

appear to be lipophilic reducing agents, including phenols, partially saturated aromatics, and compounds containing heteroatom-heteroatom bonds. However, many of these compounds are not selective 5-LO inhibitors, but often affect CO and other LOs as well. In vivo systemic activity for many of these has been in general, disappointing, probably because of poor bioavailability caused by lipophilicity and metabolic instability (oxidation, and conjugation of phenolic compounds). However, the method of administration outlined in this application, that is local and slow-release, should overcome some of these difficulties. A few structural types are selective 5-LO inhibitors which have shown systemic activity in vivo and in the clinic. Zileuton appears to be one of the leading compounds in this category, along with other hydroxamates such as BW-A4C. Recent selective non-reducing agents such as Wy-50,295 and the similar ICI compounds such as ICI 216800 also hold promise. See Batt at 32-33 and references cited therein.

While the present invention is not bound to any particular theory of operation, it is believed that 5-LO inhibitors may inhibit adhesion formation between tissue, e.g. organ, surfaces in body cavities through a variety of mechanisms. For example, 5-LO inhibitors alter arachidonic acid metabolism, which produces mediators, e.g.,leukotrienes, of an inflammatory response and thus reduces inflammation [Anderson et al. (1992) "EYTA, a pleotrophic membrane-active arachidonic acid analogue affects multiple signal transduction pathways in cultured transformed mammalian cells," Clin. Biochem., Vol. 25, pp. 1-9; Miyano and Chiou. (1984), "Pharmacological prevention of ocular inflammation induced by lens proteins", Ophthalmic Research, Vol. 16, pp. 256-263.]

In addition, leukotrienes (whose synthesis is blocked by LO inhibitors) are chemotactic for leukocytes [Musser

and Kreft (1992), "5-Lipoxygenase: Properties, pharmacology and the quinolinyl (bridged)aryl class of inhibitors", J. Med. Chem., Vol. 35, pp. 2501-2524; Gulbenkian et al. (1990), "Anaphylactic challenge causes eosinophil accumulation in bronchoalveolar lavage fluid of guinea pigs. Modulation by betamethasone, phenidone, indomethacin, WEB 2086, and a novel antiallergy agent, SCH 37224," Am. Rev. Respir. Dis., Vol. 142, pp. 680-685]. As an example, LO inhibitors reduce PMN infiltration [DeMartino et al. (1989), "The pharmacology of arachidonic acid-induced rat PMN leukocyte infiltration," Agent Action, Vol. 27, pp. 325-327]. As leukocytes are instrumental in wound repair and lysis of fibrin, these agents may affect adhesion formation through these actions on leukocyte chemotaxis.

As is well recognized in the art, however, no one of these possible mechanisms of action of 5-LO inhibitors would in and of itself be sufficient to enable one to predict whether these compounds would have any utility in reduction of adhesion formation. Indeed, several properties of 5-LO inhibitors would suggest that such compounds would be ineffective at reducing adhesion formation. For example, fibrinolysis is crucial in clearance of fibrin deposited after surgical injury. If the deposition of fibrin is prolonged, then the potential for adhesion formation is increased. NDGA inhibits the production of urokinase (a plasminogen activator), which catalyzes the cleavage of plasminogen to plasmin, a major fibrinolytic enzyme [Rondeau et al. (1990), "Nordihydroguaiaretic acid inhibits urokinase synthesis by phorbol myristate acetate-stimulated LCC-PK1 cells," BBA, Vol. 1055, pp. 165-172]. Inhibition of urokinase would be expected to promote, not diminish, fibrin deposition.

It is also known in the art that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the formation of

adhesions. NSAIDs are believed to inhibit the formation of arachidonic acid metabolites through inhibition of cyclooxygenase (CO). Some of the compounds described above and in the Examples below are capable of inhibiting CO. However, NSAIDs and the compounds that inhibit 5-LO have many distinct biological properties such that a person of ordinary skill in the art would not have any reason to believe that 5-LO inhibitors would reduce adhesion formation. 5-LO inhibitors are distinct from NSAIDs in a number of ways. For instance, NSAIDs reduce early phase of ocular inflammation. NDGA, however, inhibits both the early and late phase of ocular inflammation [Miyano and Chiou. (1984), "Pharmacological prevention of ocular inflammation induced by lens proteins", Ophthalmic Research, Vol. 16, pp. 256-263.].

NSAIDs increase urokinase production, however, lipoxygenase inhibitors do not affect or reduced urokinase production [Chow et al. (1987), "Pharmacological modulation of plasminogen activator secretion by P388D1 cell line," Agents and Actions, Vol. 21, pp. 387-389].

LO inhibitors decrease granuloma formation, however, NSAIDs have no effect on the formation of granulomas [Kunkel et al. (1984), "Role of lipoxygenase products of murine pulmonary granuloma formation," J. Clin. Invest., Vol. 74, pp. 514-524].

Additionally, LO inhibitors decrease the arachidonic acid-induced increase in myeloperoxidase, whereas NSAIDs have no effect [DiMartino et al. (1989), "The pharmacology of arachidonic acid-induced rat PMN leukocyte infiltration," Agents and Action, Vol. 27, pp. 325-327; Griswold et al. (1989), "Inhibition of inflammatory cell infiltration by bicyclic imidazoles, SK&F 86002 and SK&F 1004493," Inflammation, Vol. 13, pp. 727-739].

LO inhibitors also reduce eosinophil accumulation, while NSAIDs had no effect [Gulbenkian et al. (1990),

"Anaphylactic challenge causes eosinophil accumulation in bronchoalveolar lavage fluid of guinea pigs. Modulation by betamethasone, phenidone, indomethacin, WEB 2086, and a novel antiallergy agent, SCH 37224," Am. Rev. Respir. Dis., Vol. 142, pp. 680-685].

In addition, LO inhibitors had no effect on the biphasic response to bradykinin, but NSAIDs altered the response [Calixto and Medeiros. (1991), "Characterization of bradykinin mediating pertussis toxin-insensitive biphasic response in circular muscle of the isolate guinea pig ileum," J. Pharm. Exper. Ther., Vol. 259, pp. 659].

Accordingly, in light of these possible mechanisms of action of 5-LO inhibitors, there is no suggestion that 5-LO inhibitors would in and of itself have any utility in preventing or reducing post-surgical adhesion formation.

5-LO inhibitors phenidone, nordihydroguaiaretic acid (NDGA), 5,8,11,14-eicosatetraynoic acid (EYTA) and Zileuton have been exemplified below as useful compounds for reducing or preventing post-surgical adhesion formation. These structurally unrelated compounds share a common 5-LO inhibitory effect and other compounds which are also capable of inhibiting 5-LO activity are also contemplated for use in the present invention. In addition to the compounds described in the references cited in this application, other non-limiting examples of 5-LO inhibitors are described in U.S. Patent Nos. 5,246,948, 5,023,255, and 4,708,964; European Patent Application Nos. 0612 729 A2, published August 31, 1994 and 0146 348 A2, published June 26, 1985; and WO 95/04055, published February 9, 1995.

In practicing this invention, the preferred 5-LO inhibitor compounds are those which have little or no toxicity at the local and systemic level and are suitable for topical use in animals, including humans. Methods which may be employed in identifying compounds which inhibit 5-LO activity are disclosed, for example, in Batt

(1992), "5-Lipoxygenase inhibitors and their anti-inflammatory activities," Prog. Med. Chem., Vol. 29, pp. 1-63; Riendeau et al. (1989), "Sensitivity of immunoaffinity-purified porcine 5-lipoxygenase to inhibitors and activating lipid hydroxyperoxides," Biochem. Pharmacol., Vol. 38, pp. 2313-2321; Miyazawa et al. (1985), "Effects of some non-steroidal anti-inflammatory drugs and other agents on cycloxygenase and lipoxygenase activities in some enzyme preparations," Jap. J. Pharmacol., Vol. 38, pp. 199-205. A representative method for identifying compounds which inhibit 5-LO activity is disclosed in the Examples.

Pursuant to the method of the present invention, at least one 5-LO inhibitor is maintained in an effective concentration at the site of potential adhesion formation for a period of time sufficient to permit substantial re-epithelialization. The 5-LO inhibitor is typically administered over the perioperative interval, which for purposes of the present invention may include time shortly prior to surgery through the surgery itself up to some time after completion of surgery.

The effective therapeutic concentrations of 5-LO inhibitors is one that minimizes or prevents post-surgical adhesion formation between tissue surfaces in body cavities. Typically, the concentrations of 5-LO inhibitor which can be administered would be limited by efficacy at the lower end and the solubility of the compound at the upper end. In general, the effective therapeutic concentration of the 5-LO inhibitors is one that inhibits 5-LO activity from between about 1 to about 100%, preferably from between about 10 to about 100%.

The 5-LO inhibitor may be administered directly following the surgical procedure in a suitable vehicle, for example, a solution of saline, 5% DMSO in saline or 10% ethanol in saline, to a site at which it is desired to reduce or prevent adhesion formation. Pursuant to

preferred embodiments of the present invention, however, at least one 5-LO inhibitor is administered in a single dose delivery (for example, prior to skin closure after surgery) using a drug-delivery system which enables the maintenance of requisite concentrations of the compound for a period of time sufficient for re-epithelialization. A suitable drug-delivery system would itself be essentially non-inflammatory and non-immunogenic and would permit release of the 5-LO inhibitor so as to maintain effective levels thereof over the desired time period.

A large variety of alternatives are known in the art as suitable for purposes of sustained release and are contemplated as within the scope of the present invention. Suitable delivery vehicles include, but are not limited to, the following: microcapsules or microspheres; liposomes and other lipid-based release systems; crystalloid and viscous instillates; absorbable and/or biodegradable mechanical barriers; and polymeric delivery materials, such as polyethylene oxide/polypropylene oxide block copolymers (e.g. poloxamers), poly-orthoesters, cross-linked polyvinyl alcohol, polyanhydrides, polymethacrylate and polymethacryladmide hydrogels, anionic carbohydrate polymers, etc.. Useful delivery systems are well known in the art and are described in, e.g., U.S. Patent No. 4,937,254, the entire disclosure of which is hereby incorporated by reference.

One particularly suitable formulation to achieve the desired near pseudo zero-order release of 5-LO inhibitors comprise injectable microcapsules or microspheres prepared from a biodegradable polymer, such as poly(dl-lactide), poly(dl-lactide-co-glycolide), poly-caprolactone, polyglycolide, polylactic acid-co-glycolide, poly(hydroxybutyric acid), a polyortho-ester or a polyacetal.

Injectable systems comprising microcapsules or microspheres of a diameter on the order of about 50 to about 500 μm offer advantages over other delivery systems. For example, they generally use less active agent and may be administered by paramedical personnel. Moreover, such systems are inherently flexible in the design of the duration and rate of separate drug release by selection of microcapsule size, drug loading and dosage administered. In addition, such microcapsules can be successfully sterilized with gamma irradiation.

Microcapsules are systems comprising a polymeric wall that encloses a liquid or solid core. The capsule wall usually does not react with the core material; however, it is designed to provide sufficient strength to enable normal handling without rupture while being sufficiently thin to allow a high core to wall volume ratio. The capsule contents remain within the wall until released by diffusion or other means that dissolve, melt, break, rupture or remove the capsule material. Preferably, the capsule wall can be made to degrade and decompose in suitable environments while diffusing the core material through the capsule wall to allow for its slow, prolonged delivery.

The mechanism of release in biodegradable microcapsules is a combination of drug diffusion and polymer biodegradation. Therefore, the rate and duration of release are determined by microcapsule size, drug content and quality, and polymer parameters such as crystallinity, molecular weight and composition. In particular, adjustment in the amount of drug released is generally achieved by modification of capsule wall thickness, capsule diameter, or both. Detailed information concerning the design, preparation and use of microspheres and microcapsules is provided by, e.g., Lewis, D.H., "Controlled Release of Bioactive Agents from Lactide/Glycolide Polymers," in "Biodegradable Polymers as

Drug Delivery Systems," Jason & Langer, eds., pp. 1-41 (1990), the entire disclosure of which is hereby incorporated by reference. The sustained intraperitoneal release of dexamethasone using poly(lactide-co-glycolide) microparticles is described in Hoeckel, M. et al., "Prevention of Peritoneal Adhesions in the Rat with Sustained Intraperitoneal Dexamethasone Delivered by a Novel Therapeutic System," Annales Chirurgiae et Gynaecologiae, Vol. 76, pp. 306-313 (1987), the entire disclosure of which is also incorporated by reference.

As is well known to those skilled in the art, various methods are currently available for preparing microcapsules, any of which could be employed to provide formulations in accordance with the present invention. Biodegradable polymeric materials suitable for preparation of microcapsules for controlled (i.e., near zero-order) release would be readily determined through routine experimentation by those skilled in the art. Moreover, alternative delivery systems suitable for use in accordance with the present invention (for example, fibers or filaments comprising the active agents) based on biodegradable polymers are also contemplated as within the scope of the present invention.

An alternative approach for the single-dose delivery of at least one 5-LO inhibitor involves the use of biodegradable polymers, such as the ones described above, in the form of a film. Such films may be produced by spraying or discharging dispersed liquid droplets containing the biopolymer and the 5-LO inhibitor in a suitable carrier from a pressurized container onto the targeted site.

Another approach for the single-dose delivery of at least one 5-LO inhibitor, in accordance with the present invention, involves the use of liposomes and other lipid-based delivery systems. The encapsulation of an active

agent in multilamellar vesicles (or liposomes) is a well known technique used to assist in target drug delivery and prolong drug residence. In a typical procedure, a liposome-forming powdered lipid mixture is added to the desired quantity of active agent in aqueous solution (e.g., phosphate buffered saline) to form a suspension. After a suitable hydration period, the hydrated suspension is then autoclaved to provide the liposome-active agent preparations. A lipid mixture suitable for formation of liposomes may be prepared from L-alpha-distearoyl phosphatidylcholine and cholesterol dissolved in chloroform, to which alpha-tocopherol is added; other compositions and methods for formation of liposomes would, however, also be useful for this purpose. The intraperitoneal administration of liposomes containing ibuprofen or tolmetin is described in Rodgers, K. et al., "Inhibition of Postsurgical Adhesions by Liposomes Containing Nonsteroidal Anti-inflammatory Drugs," Int. J. Fertil., Vol. 35, p. 40 (1990), the entire disclosure of which is hereby incorporated by reference.

Other lipid-based delivery systems are also contemplated for use in this invention. One useful system includes lipid foams such as DepoFoam extended-release formulations comprising spherical particles bounded by a single bilayer lipid membrane and each containing numerous nonconcentric aqueous chambers which encapsulate the active ingredient (see, e.g, Kim, T.K. et al. (1993) "Extended-release formulation of morphine for subcutaneous administration," Cancer Chemother. Pharmacol., Vol. 33, 187; Chatelut, E. et al. (1993) "A slow-release methotrexate formulation for intrathecal chemotherapy," Cancer Chemother. Pharmacol., Vol. 32, 179.] Such lipid particles are made from nontoxic lipids identical to those found in cell membranes.

Another suitable lipid-based delivery system for delivering the 5-LO inhibitors according to the invention includes emulsion carrier systems based on egg sphinomyelin and egg phosphatidylcholine. Such emulsion carrier systems have prolonged blood circulation retention times and were developed for delivering highly lipophilic drugs. T. Takino et al. (1994) "Long Circulating Emulsion Carrier Systems for Highly Lipophilic Drugs," Biol. Pharm. Bull., Vol. 17, pp. 121-125.

Yet another suitable approach for single dose delivery of at least one 5-LO inhibitor in accordance with the present invention involves the use of crystalloid or so-called viscous instillates. Crystalloids are known in the art as water soluble crystalline substances, e.g. NaCl, capable of diffusing through a semi-permeable membrane. Solutions of crystalloids, such as saline, are known as crystalloids, crystalloid solutions or crystalloid instillates. Crystalloids include, but are not limited to, phosphate buffered saline, saline or lactated Ringer's solution. High-molecular-weight viscous carriers used in admixture with the active agents include, but are not limited to, the following: dextrans and cyclodextrans; hydrogels; cross-linked viscous materials, including viscoelastics and cross-linked viscoelastics; carboxymethylcellulose; hyaluronic acid, crosslinked hyaluronic acid, and hyaluronic acid compounded with orthoesters. While some studies have suggested that the use of viscous barrier solutions per se may have an advantageous effect in reducing the incidence of adhesion formation, it is believed that any such effect is of limited scope when compared to the combination of at least one 5-LO inhibitor and carrier. The intraperitoneal administration of a viscous instillate comprising tolmetin is described in Abe, H. et al., "The Effect of intra-peritoneal Administration of Sodium Tolmetin-Hyaluronic

Acid on the Postsurgical Cell Infiltration *In Vivo*," J Surg. Res., Vol. 49, p. 322 (1990), the entire disclosure of which is hereby incorporated by reference.

Pursuant to yet another approach, at least one 5-LO inhibitor is administered in combination with an absorbable mechanical barrier which alone reduces adhesion formation. As would be readily apparent to one working in the field, at least one 5-LO inhibitor may be covalently or non-covalently (e.g., ionically) bound to such a barrier, or it may simply be dispersed therein. A particularly suitable vehicle for use in this particular embodiment of the invention comprises hydroxyethyl starch which is described in U.S. Patent application Ser. No. 08/482,235, filed concurrently with this application, entitled HYDROXYETHYL STARCH AND USE THEREOF AS AN ABSORBABLE MECHANICAL BARRIER AND INTRACAVITY CARRIER DEVICE by Gere diZerega (University of Southern California, assignee), and incorporated by reference in its entirety.

Another suitable mechanical barrier for use in this invention includes oxidized regenerated cellulose which is available under the designation INTERCEED(TC7) from Johnson and Johnson Medical, Inc., New Brunswick, New Jersey [INTERCEED(TC7) Adhesion Barrier Study Group, "Prevention of postsurgical adhesions by INTERCEED(TC7), an absorbable adhesion barrier: a prospective, randomized multicenter clinical study," Fertility and Sterility, Vol. 51, p. 933 (1989)]. The use of a mechanical barrier as a carrier to deliver heparin to traumatized surfaces is disclosed in Diamond, M. P. et al., "Synergistic effects of INTERCEED(TC7) and heparin in reducing adhesion formation in the rabbit uterine horn model," Fertility and Sterility, Vol. 55, p. 389 (1991) and Diamond, M.P. et al., "Adhesion reformation: reduction by the use of INTERCEED(TC7) plus heparin," J. Gyn. Surg., Vol. 7, p. 1 (1991), the entire disclosures of which are hereby incorporated by reference.

The invention may be better understood with reference to the accompanying examples, which are intended to be illustrative only and should not be viewed as in any sense limiting the scope of the invention, which is defined hereinafter in the accompanying claims.

EXAMPLES

Multiple studies to confirm the efficacy of 5-lipoxygenase inhibitors in the reduction of adhesion formation after peritoneal surgery were performed. Two model systems were employed: the sidewall adhesion model and the uterine horn model. A clear correlation between results obtained using both of these models and utility in adhesion prevention has been demonstrated with INTERCEED(TC7), for which clear clinical efficacy has been shown and FDA approval for adhesion prevention in gynecological surgery has been obtained.

In the peritoneal sidewall model, rabbits were pre-anesthetized with 1.2 mg/kg acetylpromazine and anesthetized with a mixture of 55 mg/kg ketamine hydrochloride and 5 mg/kg xylazine intramuscularly. Following preparation for sterile surgery, a midline laparotomy was performed. A 3 x 5-cm area of peritoneum and transversus abdominis muscle was removed on the right lateral abdominal wall. The cecum was exteriorized, and digital pressure was exerted to create subserosal hemorrhages over all cecal surfaces. The cecum was then returned to its normal anatomic position. The compound to be tested was placed in an Alzet miniosmotic pump (Alza Corporation, Palo Alto, CA, USA) to allow continuous release of the molecule through the postsurgical interval. The Alzet miniosmotic pump was placed in the subcutaneous space and a delivery tube connected the pump with the site of injury at sidewall. Vehicle was placed in the pump of control rabbits. The abdominal wall and skin were closed

in a standardized manner.

After 7 days, the rabbits were sacrificed and the percentage of the area of the sidewall injury that is involved in adhesions was determined. In addition, the tenacity of the adhesion formed was scored use a system as follows:

0 = No adhesions

1 = mild, easily dissectable adhesions

2 = moderate adhesions; non-dissectable, does not tear organ

3 = dense adhesions; non-dissectable, tears when removed

A reduction in the area or the tenacity of the adhesions would be considered beneficial.

In additional experiments, a rabbit uterine horn model was employed. This model has been previously shown to cause severe adhesions in rabbits after surgery [Nishimura, K. et al., "The Use of Ibuprofen for the Prevention of Postoperative Adhesions in Rabbits," Am. J. Med., Vol. 77, pp. 102-106 (1984)]. The rabbits were anesthetized (130 mg/kg ketamine and 20 mg/kg acetylpromazine im) and prepared for sterile surgery. A midline laparotomy was performed, and surgical trauma was performed on both uterine horns by abrading the serosal surface with gauze until punctate bleeding developed. Ischemia of both uterine horns was induced by removal of the collateral blood supply. After traumatization, the abdominal wall was closed in two layers. The inhibitor to be tested was delivered as described for the peritoneal sidewall model, but the tubing was placed over the injured uterine horns.

With the uterine horn model, an initial score to represent the overall extent of adhesions is given (0 to 4+). The percentage of a surface of the horn involved in adhesions to various organs are given in the tables below

the overall adhesion score.

In the model systems employed in the examples reported herein, exemplary 5-lipoxygenase inhibitor compounds phenidone, NDGA, Zileuton, and ETYA were shown to reduce the incidence of peritoneal adhesions. In these Examples, the drug was delivered to the targeted site at a rate of 10 μl/hour. The concentration ranges employed were 0.0001 to 0.5 mg/ml. For purposes of preventing adhesion formation in accordance with the present invention, it is not believed that high systemic levels of 5-lipoxygenase inhibitors would be necessary.

EXAMPLE 1: General 5-LO Activity Assay Procedure

In this Example, a assay procedure is provided to identify compounds that inhibit 5-LO activity. According to the procedure as disclosed by Riendeau et al. (1989), "Sensitivity of immunoaffinity-purified porcine 5-lipoxygenase to inhibitors and activating lipid hydroxyperoxides," Biochem. Pharmacol., Vol. 38, pp. 2313-2321. 5-Lipoxygenase activity is measured from the increase in absorbance at 235nm following incubation of 5-LO, isolated from porcine leukocytes, arachidonic acid, ATP and calcium. The standard reaction mixture contains 0.55 M Tris-HCl, pH 7.4, 0.2 mM ATP, 0.4 mM $CaCl_2$, 20 or 27 mM arachidonic acid (5 μl of a 100-fold concentrated solution in ethanol), 24 μg/ml phosphatidylcholine, and an aliquot of the enzyme preparation (5-75 μl) in a final volume of 0.5 ml. The volume of enzyme is completed to 100 μl using a chromatography elution buffer (50 mM sodium carbonate, pH 10, containing 0.2% sodium deoxycholate, 0.5 mM dithiothreitol and 1 mM EDTA into 0.5 M Tris). The buffer solution containing $CaCl_2$ (0.4 M) and phosphotidylcholine (24 μg/ml) is filtered through 0.2 μm Nalgene filters.

The assay reactions are performed in semi-micro cuvettes (1.4 ml capacity, 100 mm path length and 4 mm

internal width) and initiated by the addition of the enzyme to the assay mixture. The reaction mixture is gently mixed with a Pasteur pipet (15 sec) before recording the variation in A235 as a function of time at room temperature.

EXAMPLE 2: Sidewall Model Evaluation of Phenidone

The efficacy of phenidone (Sigma Chemical Co., St. Louis, MO), a 5-LO inhibitor discussed above, in preventing adhesion formation was evaluated at two doses in a sidewall model. The drug was delivered for 7 days at a rate of 10 µl/hr and the animals were sacrificed after 7 days. The vehicle used was saline. Relative to the control, phenidone was found to be efficacious in 5 of 6 rabbits at the high dose and in 4 of 6 rabbits in the lower dose. No inflammation or precipitation noted at the site of injury. The results are summarized in Table 1. A student t test analysis of the data was performed and the results are also reported in Table 1.

TABLE 1

TREATMENT	% ADHESIONS	ADHESION SCORE
Vehicle Control	80%	2+
	60%	3+
	60%	2+
	70%	2+
	50%	2+
	100%	3+
Mean:	70.0% ± 17.8%	
0.5 mg/ml Phenidone	40%	2+
	10%	1+
	80%	2+
	30%	1+
	10%	1+
	0%	0+
Mean[a]:	28.3% ± 29.3%	
0.05 mg/ml Phenidone	70%	1+
	100%	3+
	0%	0+
	0%	0+
	10%	1+
	40%	2+
Mean[b]:	36.7% ± 41.3%	

a: $p = 0.014$
b: $p = 0.100$

EXAMPLE 3: Sidewall model evaluation of NDGA

The efficacy of nordihydroguaiaretic acid (NDGA) (available from Sigma Chemical, St. Louis, MO), a 5-LO inhibitor discussed above, in preventing adhesion formation was evaluated at two doses in a sidewall model. The drug was delivered for 7 days at a rate of 10 µl/hr and the animals were sacrificed after 7 days. The vehicle used was 0.1% ethanol in saline, pH 10.3. Relative to the control, NDGA appears to be efficacious in 5 of 6 rabbits at the high dose and in 3 of 5 rabbits in lower dose. No inflammation or precipitation noted at the site of injury. The results are summarized in Table 2. A student t test analysis of the data was performed and the results are also reported in Table 2.

TABLE 2

TREATMENT	% ADHESIONS	ADHESION SCORE
Vehicle Control	90%	2+
	Died due to bowel obstruction due to adhesions	
	100%	3+
	90%	3+
	40%	3+
	100%	2+
Mean:	84.0% ± 25.1%	
0.3 mg/ml NDGA	30%	2+
	30%	2+
	0%	0+
	60%	1+
	0%	0+
	0%	0+
Mean[a]:	20.0% ± 24.5%	
0.03 mg/ml NDGA	100%	3+
	10%	1+
	20%	1+
	70%	2+
	0%	0+
	Died on Day 5 P/O	
Mean[b]:	40.0% ± 43.0%	

a: $p = 0.002$
b: $p = 0.084$

EXAMPLE 4: Sidewall Model evaluation of ETYA

The efficacy of 5,8,11,14-eicosatetraynoic acid (ETYA) (available from Sigma Chemical, St. Louis, MO), a 5-LO inhibitor discussed above, in preventing adhesion formation was evaluated at two doses in a sidewall model. The drug was delivered for 7 days at a rate of 10 µl/hr and the animals were sacrificed after 7 days. The vehicle used was 11.1% ethanol in saline, pH 10.6. Relative to the control, ETYA was efficacious in the prevention of adhesions in this rabbit sidewall model. The results are summarized in Table 3. A student t test analysis of the data was performed and the results are also reported in Table 3.

TABLE 3

TREATMENT	% ADHESIONS	ADHESION SCORE
Vehicle Control	40%	3+*
	100%	3+*
	70%	3+
	70%	2+
	80%	3+
	50%	2+
Mean:	68.3% ± 21.4%	
0.1 mg/ml ETYA	30%	2+*
	Died	
	0%	0+
	0%	0+
	5%	1+
	10%	0+
Mean:	9.0% ± 12.5%	
0.01 mg/ml ETYA	100%	3+*
	40%	1+
	40%	1+
	Died	
	0%	0+
	30%	1+
Mean:	42.0% ± 36.0%	

a: p = 0.000
b: p = 0.169

* Sidewall was inflamed.

EXAMPLE 5: DUH Model Evaluation of Phenidone

The efficacy of phenidone, the compound exemplified in Example 2 above, in preventing adhesion formation was evaluated at two doses in a double uterine horn (DUH) model. The drug was delivered for 7 days at a rate of 10 μl/hr and the animals were sacrificed after 7 days. The vehicle used was saline. Statistical analysis was performed on the overall score of the nonparametric double uterine horn model data. The data was rank ordered, a rank value was given and an analysis of variance on the ranks was performed. The results are summarized in Tables 4 and 5. Relative to the control, phenidone was efficacious in reducing adhesion formation in this model.

TABLE 4

TREATMENT	OVERALL ADHESION SCORE
Vehicle Control	3+
	3.5+
	3.5+
	3+
	3+
	3.5+
0.5 mg/ml Phenidone	1+
	2+
	2+
	0.5+
	1.5+
	1+
0.05 mg/ml Phenidone	2+
	2+
	1+
	1.5+
	2+
	1.5+

TABLE 5
% Organ Involvement in Uterine Horn Adhesion

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
Control	60	50	50	50	60	50	40	50
	40	80	40	40	40	80	40	40*
	60	40	60	50	60	40	50	50*
	50	40	100	30	50	40	40	30*
	20	100	40	50	20	100	40	50*
	50	60	80	30	50	50	60	30
Mean	46.7	60	61.7	41.7	46.7	60	45	41.7
0.5 mg/ml Phenidone	10	0	10	0	10	0	0	0
	0	0	40	40	0	0	40	40
	0	0	30	30	0	40	40	30
	10	0	20	0	0	0	0	0
	0	0	10	0	0	0	0	0*
	0	10	0	40	0	10	0	40
Mean	3.3	1.7	18.3	18.3	1.7	8.3	13.3	18.3
0.05 mg/ml Phenidone	10	10	40	10	10	10	0	10
	20	0	30	10	20	0	30	10
	0	0	20	0	0	20	40	0
	20	20	10	0	20	20	20	0
	30	0	30	0	30	0	60	0*
	100	0	10	0	100	0	0	0*
Mean	30	5	23.3	3.3	30	8.3	25	3.3

* Bladder, horn and/or bowel adhered to the sidewall at the suture for the tube.

Statistical analysis was performed on the overall score of the nonparametric data taken from Table 4. The data was rank ordered and assigned a rank value. Analysis of the variance of the ranks was then performed and the resulting student t test results are summarized below.

Treatment	Rank order	p value
Control	15.5 ± 1.5	---
0.5 mg/ml phenidone	5.5 ± 3.5	0.000
0.05 mg/ml phenidone	7.5 ± 2.7	0.000

EXAMPLE 6: DUH Model Evaluation of NDGA

The efficacy of NDGA, the compound exemplified in Example 3 above, in preventing adhesion formation was evaluated at two doses in a double uterine horn model. The drug was delivered for 7 days at a rate of 10 µl/hr and the animals were sacrificed after 7 days. The vehicle used was 0.1% ethanol in saline, pH 10.3. Statistical analysis was performed on the overall score of the nonparametric double uterine horn model data. The data was rank ordered, a rank value was given and an analysis of variance on the ranks was performed. The results are summarized in Tables 6 and 7. Relative to the control, NDGA was efficacious in reducing adhesion formation in this model.

TABLE 6

TREATMENT	OVERALL ADHESION SCORE
Vehicle Control	3+
	3+
	3.5+
	3.5+
	3+
	3.5+
0.3 mg/ml NDGA	1.5+
	1.5+
	1.5+
	Infection
	2.5+
	2+
0.03 mg/ml NDGA	2+
	2+
	1.5+
	1.5+
	2.5+
	1.5+

TABLE 7
% Organ Involvement in Uterine Horn Adhesion

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
Control	60	0	50	50	60	0	40	50**
	40	50	40	50	40	50	40	50*
	30	40	40	50	30	40	40	50**
	100	10	40	50	100	10	40	50**
	30	40	50	60	30	40	50	60**
	50	40	60	50	50	40	60	50**
Mean	51.7	30	46.7	51.7	51.7	30	45	51.7
0.3 mg/ml NDGA	0	40	30	0	0	40	0	0
	30	0	30	0	30	0	0	0*
	0	0	10	0	50	0	0	0*
					INFECTION			
	40	30	0	0	40	30	0	0**
	30	20	0	10	30	20	20	10*
Mean	20	18	14	2	30	18	4	2
0.03 mg/ml NDGA	0	0	20	30	0	0	30	30**
	30	10	0	0	30	10	20	0*
	0	0	40	0	0	0	50	0*
	40	0	20	0	40	0	0	0
	30	30	0	0	30	30	30	0*
	0	10	30	0	0	10	0	0
Mean	16.7	8.3	18.3	5	16.7	8.3	21.7	5

* Bladder and/or bladder adhered to sidewall at the tube or suture for the tube.

** Horn along with bowel and/or bladder adhered to sidewall at the tube or the suture for the tube.

Statistical analysis was performed on the overall score of the nonparametric data taken from Table 6. The data was rank ordered and assigned a rank value. Analysis of the variance of the ranks was then performed and the resulting student t test results are summarized below.

Treatment	Rank order	p value
Control	14.5 ± 1.5	---
0.3 mg/ml NDGA	5.8 ± 2.9	0.000
0.03 mg/ml NDGA	6.2 ± 2.8	0.000

EXAMPLE 7: DUH Model Evaluation of ETYA

The efficacy of ETYA, the compound exemplified in Example 4 above, in preventing adhesion formation was evaluated at two doses in a double uterine horn model. The drug was delivered for 7 days at a rate of 10 μl/hr and the animals were sacrificed after 7 days. The vehicle used was 11.1% ethanol in saline, pH 10.6. Statistical analysis was performed on the overall score of the double uterine horn model nonparametric data. The data was rank ordered, a rank value was given and an analysis of variance on the ranks was performed. The results are summarized in Tables 8 and 9. Relative to the control, ETYA was efficacious in the reduction of adhesion formation in this model.

TABLE 8

TREATMENT	OVERALL ADHESION SCORE
Vehicle Control	2.5+
	3+
	3.5+
	3+
	3.5+
	3+
0.1 mg/ml ETYA	2+
	1.5+
	1+
	1.5+
	1.5+
	1.5+
0.01 mg/ml ETYA	0.5+
	1+
	1+
	1+
	0.5+
	1+

TABLE 9
% Organ Involvement in Uterine Horn Adhesion

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
Control	40	50	30	40	40	50	30	40**
	30	70	50	60	30	70	50	60
	30	60	40	50	30	60	40	50**
	20	30	40	50	20	30	40	50
	80	70	40	30	80	70	30	30**
	40	60	60	50	40	60	40	50**
Mean	40	56.7	43.3	46.7	40	56.7	38.3	46.7
0.1 mg/ml ETYA	30	20	20	40	30	0	20	40
	10	0	40	0	10	0	0	0
	0	0	30	0	10	0	10	0
	10	20	30	0	0	20	20	0
	30	0	40	0	30	0	20	0
	30	0	20	10	30	0	0	10
Mean	18.3	6.7	30	8.3	18.3	3.3	11.7	8.3
0.01 mg/ml ETYA	0	0	10	0	0	0	10	0*
	0	0	40	0	0	0	40	0
	0	0	30	0	0	0	0	0*
	10	0	30	0	0	0	0	0
	0	0	10	0	0	0	0	0
	0	20	0	0	0	20	20	0
Mean	1.7	3.3	20	0	0	3.3	11.7	0

* Bowel and/or bladder adhered to sidewall at the tube or suture for the tube.

** Horn along with bowel and/or bladder adhered to sidewall at the tube or the suture for the tube.

Statistical analysis was performed on the overall score of the nonparametric data taken from Table 8. The data was rank ordered and assigned a rank value. Analysis of the variance of the ranks was then performed and the resulting student t test results are summarized below.

Treatment	Rank order	p value
Control	15.5 ± 1.6	---
0.1 mg/ml ETYA	9.2 ± 2.1	0.000
0.01 mg/ml ETYA	3.8 ± 1.7	0.000

EXAMPLE 8: Kinetic DUH Model evaluation of ETYA

The efficacy of ETYA in the rabbit double uterine horn model was further evaluated in a kinetics study. In this study, the pump was disconnected (D/C) at various times after surgery (24, 48, or 72 hours) to determine the time period of exposure to the drug effective to reduce adhesion formation. The results are summarized in Tables 10 and 11.

TABLE 10

TREATMENT	OVERALL ADHESION SCORE
Vehicle Control	3+
	2.5+
	3+
	2.5+
	3.5+
	3.5+
0.1 mg/ml ETYA 24 hour D/C	1.5+
	1.5+
	1.5+
	1.5+
	0.5+
	0.5+
0.1 mg/ml ETYA 48 hour D/C	1+
	2+
	1+
	1+
	1+
	2+
0.1 mg/ml ETYA 72 hour D/C	0.5+
	1.5+
	1.5+
	1.5+
	1.5+

TREATMENT	OVERALL ADHESION SCORE
	2+
0.01 mg/ml ETYA 24 hour D/C	1+
	Infection
	0.5+
	1.5+
	0.5+
	1.5+
0.01 mg/ml ETYA 48 hour D/C	1+
	1+
	1+
	1.5+
	2+
	0.5+
0.01 mg/ml ETYA 72 hour D/C	1+
	0.5+
	1.5+
	1+
	1+
	1+

TABLE 11
% Organ Involvement in Uterine Horn Adhesion

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
Control	50	10	20	30	50	10	40	30**
	10	20	40	50	10	20	30	50
	50	40	40	40	50	40	40	40**
	30	40	40	30	30	40	30	30
	80	40	40	50	80	40	40	50
	80	50	40	40	80	50	40	40*
Mean	50	33.3	36.7	40	50	33.3	36.7	40
0.1 mg/ml ETYA 24 D/C	10	0	20	10	10	0	20	10
	10	10	0	0	10	10	30	0
	30	10	20	0	30	0	0	0*
	0	10	20	10	0	10	10	10
	0	10	0	0	0	10	10	0*
	0	0	0	0	20	0	0	0**
Mean	8.3	6.7	10	3.3	8.3	5	11.7	3.3
0.1 mg/ml ETYA 48 D/C	10	0	10	0	10	0	10	0
	30	0	20	30	30	0	10	30*
	30	0	0	0	30	0	10	0
	10	0	10	0	10	0	0	0*
	20	0	20	0	20	0	0	0
	20	20	20	10	20	20	0	10
Mean	20	3.3	13.3	6.7	20	3.3	5	6.7
0.1 mg/ml ETYA 72 D/C	0	0	10	10	0	0	0	10
	10	10	10	0	10	10	10	0
	20	10	10	0	20	10	40	0

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
	10	0	0	20	10	0	20	20
	0	30	10	20	0	30	0	30*
	20	0	40	20	20	0	30	20**
Mean	10	8.3	13.3	11.7	10	8.3	16.7	13.3
0.01 mg/ml ETYA 24 D/C	0	0	30	10	0	0	30	10
				INFECTION				
	0	0	20	0	0	0	20	0
	0	10	10	20	0	10	10	20
	0	0	10	0	0	0	0	0
	20	0	10	10	20	0	30	10**
Mean	4	2	16	8	4	2	18	8
0.01 mg/ml ETYA 48 D/C	10	0	0	0	10	0	10	0
	10	0	0	10	10	0	0	10
	10	0	0	0	10	0	10	0*
	0	0	30	20	0	0	30	20
	30	20	0	20	30	20	0	20*
	0	0	30	0	10	0	0	0
Mean	10	3.3	10	8.3	11.7	3.3	8.3	8.3
0.01 mg/ml ETYA 72 D/C	0	0	20	40	0	0	20	40
	0	0	20	0	0	0	0	0
	5	10	20	10	5	10	0	10
	0	0	20	30	0	0	20	30
	20	0	20	0	20	0	10	0
			Left Horn Only in Rabbit		20	0	20	0
Mean	5	2	20	16	7.5	1.7	11.7	13.3

* Bladder and/or bowel adhered to sidewall (either at the tube or suture).

** Horn and bowel or bladder to sidewall.

Statistical analysis was performed on the overall score of the nonparametric data taken from Table 10. The data was rank ordered and assigned a rank value. Analysis of the variance of the ranks was then performed and the resulting student t test results are summarized below.

Treatment	Rank order	p value
Control	38.5 ± 1.6	---
0.1 mg/ml ETYA (24 hr)	18.3 ± 10.1	0.000
0.1 mg/ml ETYA (48 hr)	20.2 ± 9.4	0.000
0.1 mg/ml ETYA (72 hr)	25.3 ± 9.1	0.002
0.01 mg/ml ETYA (24 hr)	14.5 ± 9.6	0.000
0.01 mg/ml ETYA (48 hr)	17.3 ± 9.6	0.000
0.01 mg/ml ETYA (72 hr)	13.9 ± 6.2	0.000

EXAMPLE 9: Dose Response Study of ETYA in the DUH Model

A dose response study with ETYA was then conducted in the double uterine horn model to better define the ranges over which an inhibitor of 5-LO would be efficacious in the reduction of adhesion formation. The conditions are the same as described in Example 7. The results are summarized in Tables 12 and 13.

TABLE 12

TREATMENT	OVERALL ADHESION SCORE
Vehicle Control	3+
	2.5+
	3+
	3+
	3.5+
	3.5+
0.1 mg/ml ETYA	1+
	1.5+
	1+
	0.5+
	2+
	0.5+
0.01 mg/ml ETYA	1.5+
	1.5+
	1.5+
	1.5+
	1.5+
	0.5+
0.001 mg/ml ETYA	1.5+
	2.5+
	2.5+
	2.5+
	0.5+
	3+

TREATMENT	OVERALL ADHESION SCORE
0.0001 mg/ml ETYA	3+
	1+
	3.5+
	1+
	2+
	2+

TABLE 13
% Organ Involvement in Uterine Horn Adhesion

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
Control	50	80	100	0	50	80	50	0
	30	0	40	0	30	0	40	0**
	50	30	60	100	50	30	60	100**
	40	10	20	30	40	10	30	30**
	80	30	60	50	80	30	70	50**
	80	80	40	30	80	80	40	30**
Mean	55	38.3	53.3	35	55	38.3	48.3	46.7
0.1 mg/ml ETYA	10	10	20	0	10	0	0	0*
	10	0	30	20	10	0	30	20
	10	0	30	0	10	0	0	0*
	0	0	0	0	0	0	20	0
	30	0	50	20	30	0	50	20
	0	10	10	0	0	10	0	0
Mean	10	3.3	23.3	6.7	10	1.7	16.7	6.7
0.01 mg/ml ETYA	10	0	40	20	10	0	30	20*
	0	30	0	10	0	30	30	10*
	10	0	30	10	10	0	40	10*
	10	0	40	20	10	0	40	20
	10	0	0	30	10	0	30	30
	0	10	10	0	0	10	0	0
Mean	6.7	6.7	20	15	6.7	6.7	28.3	15
0.001 mg/ml ETYA	0	0	50	0	0	0	50	0**
	40	20	10	0	40	20	30	0**
	30	10	10	0	30	10	30	0**

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
	10	80	0	0	10	80	60	0
	0	0	10	0	0	0	10	0**
	70	50	0	50	70	50	30	50**
Mean	25	26.7	13.3	8.3	25	26.7	35	8.3
0.0001 mg/ml ETYA	20	40	50	30	20	40	20	30*
	10	0	10	10	10	0	10	10
	60	60	40	40	60	60	50	40*
	20	0	0	20	20	0	30	20
	30	50	0	0	30	50	20	0
	40	0	60	0	40	0	0	0
Mean	30	25	26.7	16.7	30	25	21.7	16.7

* Bowel and/or bladder adhered to sidewall at the tube or suture for the tube.

** Horn along with bowel and/or bladder adhered to sidewall at the tube or the suture for the tube.

Statistical analysis was performed on the overall score of the nonparametric data taken from Table 12. The data was rank ordered and assigned a rank value. Analysis of the variance of the ranks was then performed and the resulting student t test results are summarized below.

Treatment	Rank order	p value
Control	25.6 ± 2.9	---
0.1 mg/ml ETYA	7.8 ± 5.2	0.000
0.01 mg/ml ETYA	10.4 ± 3.5	0.000
0.001 mg/ml ETYA	16.8 ± 7.5	0.023
0.0001 mg/ml ETYA	16.8 ± 8.4	0.036

EXAMPLE 10: Sidewall Model Evaluation of Zileuton

The fficacy of Zileuton, a 5-LO inhibitor discussed above, in preventing adhesion formation was evaluated at two doses in a sidewall model. The drug was delivered for 7 days at a rate of 10 µl/hr and the animals were sacrificed after 7 days. The vehicle used was saline. Relative to the control, Zileuton was found to be efficacious at both concentrations tested. No inflammation or precipitation noted at the site of injury. The results are summarized in Table 14. A student t test analysis of the data was performed and the results are also reported in Table 14.

TABLE 14

TREATMENT	% ADHESIONS	ADHESION SCORE
Vehicle Control	100%	2+
	100%	3+
	100%	3+
	100%	2+
	70%	3+
	Died	
Mean:	94.0% ± 13.42%	
0.2 mg/ml Zileuton	80%	2+
	10%	1+
	50%	2+
	20%	2+
	10%	2+
	0%	0+
Mean:[a]	28.3% ± 30.6%	
0.02 mg/ml Zileuton	20%	1+
	Died	
	80%	1+
	10%	1+
	60%	1+
	20%	1+
Mean:[b]	38.0 ± 30.3	

a: $p = 0.002$
b: $p = 0.005$

While the fundamental novel features of the invention has been shown and described, it will be understood that various omissions, substitutions and changes in the form and details illustrated may be made by those skilled in the art without departing from the spirit of the invention. It is the intention, therefore, to be limited only as indicated by the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method for reducing or preventing post-surgical adhesion formation between tissue surfaces in a body cavity comprising administering an effective therapeutic amount of a 5-lipoxygenase inhibitor for a period of time sufficient to permit tissue repair.

2. The method according to claim 1, wherein said tissue repair comprises re-epithelization.

3. The method according to claim 1, wherein said tissue repair comprises mesothelial repair.

4. The method according to claim 1 wherein said 5-lipoxygenase inhibitor comprises phenidone, NDGA, EYTA or Zileuton.

5. The method according to claim 1, wherein the 5-lipoxygenase inhibitor is administered in conjunction with a delivery vehicle.

6. The method according to claim 5, wherein said delivery vehicle is in the form of microcapsules or microspheres.

7. The method according to claim 6, wherein the microcapsules or microspheres comprise a biodegradable polymer selected from the group consisting of poly(dl-lactides), poly(dl-lactide-co-glycolides), polycaprolactones, polyglycolides, polylactic acid-co-glycolides, poly(hydroxybutyric acids), polyortho-esters, polyacetals and mixtures thereof.

8. The method according to claim 5, wherein said delivery vehicle is in the form of a film.

9. The method according to claim 8, wherein the film comprises a biodegradable polymer selected from the group consisting of poly(dl-lactides), poly(dl-lactide-co-glycolides), polycaprolactones, polyglycolides, polylactic acid-co-glycolides, poly(hydroxybutyric acids), polyortho-esters, polyacetals and mixtures thereof.

10. The method according to claim 5, wherein said delivery vehicle is in the form of a liposome.

11. The method according to claim 10, wherein the liposome comprises L-alpha-distearoyl phosphatidylcholine.

12. The method according to claim 5, wherein said delivery vehicle is in the form of a lipid foam.

13. The method according to claim 5, wherein said delivery vehicle is in the form of an instillate.

14. The method according to claim 13, wherein the instillate comprises a crystalloid carrier selected from the group consisting of phosphate buffered saline, saline, and lactated Ringer's solution.

15. The method according to claim 13, wherein the instillate comprises a high-molecular-weight carrier selected from the group consisting of dextrans, cyclodextrans, hydrogels, carboxymethylcellulose, hyaluronic acid, crosslinked hyaluronic acid, hyaluronic acid compounded with orthoesters, chondroitin sulfate and mixtures thereof.

16. The method according to claim 1, wherein said 5-lipoxygenase inhibitor is administered in combination with an absorbable mechanical barrier.

17. The method according to claim 16, wherein the absorbable mechanical barrier comprises hydroxyethyl starch.

18. The method according to claim 16, wherein the absorbable mechanical barrier comprises oxidized regenerated cellulose.

19. The method according to claim 1, wherein the 5-lipoxygenase inhibitor is administered in an amount which inhibits 5-lipoxygenase activity from between about 1% to about 100%.

20. The method according to claim 19, wherein the 5-lipoxygenase inhibitor is administered in an amount which inhibits 5-lipoxygenase activity from between about 10% to about 100%.

21. A composition for use in reducing or preventing formation of post-surgical adhesions comprising a 5-lipoxygenase inhibitor.

22. The composition according to claim 21 wherein said 5-lipoxygenase inhibitor comprises phenidone, NDGA, EYTA or Zileuton.

23. The composition according to claim 21, wherein the 5-lipoxygenase inhibitor is administered in conjunction with a delivery vehicle.

24. The composition according to claim 23, wherein said delivery vehicle is in the form of microcapsules or microspheres.

25. The composition according to claim 24, wherein the microcapsules or microspheres comprise a biodegradable polymer selected from the group consisting of poly(dl-lactides), poly(dl-lactide-co-glycolides), polycaprolactones, polyglycolides, polylactic acid-co-glycolides, poly(hydroxybutyric acids), polyortho-esters, polyacetals and mixtures thereof.

26. The composition according to claim 23, wherein said delivery vehicle is in the form of a film.

27. The composition according to claim 26, wherein the film comprises a biodegradable polymer selected from the group consisting of poly(dl-lactides), poly(dl-lactide-co-glycolides), polycaprolactones, polyglycolides, polylactic acid-co-glycolides, poly(hydroxybutyric acids), polyortho-esters, polyacetals and mixtures thereof.

28. The composition according to claim 23, wherein said delivery vehicle is in the form of a liposome.

29. The composition according to claim 28, wherein the liposome comprises L-alpha-distearoyl phosphatidylcholine.

30. The composition according to claim 23, wherein said delivery v hicle is in the form of a lipid foam.

31. The composition according to claim 23, wherein said delivery vehicle is in the form of an instillate.

32. The composition according to claim 31, wherein the instillate comprises a crystalloid carrier selected from the group consisting of phosphate buffered saline, saline, and lactated Ringer's solution.

33. The composition according to claim 31, wherein the instillate comprises a high-molecular-weight carrier selected from the group consisting of dextrans, cyclodextrans, hydrogels, carboxymethylcellulose, hyaluronic acid, crosslinked hyaluronic acid, hyaluronic acid compounded with orthoesters, chondroitin sulfate and mixtures thereof.

34. The composition according to claim 21, wherein said 5-lipoxygenase inhibitor is administered in combination with an absorbable mechanical barrier.

35. The composition according to claim 34, wherein the absorbable mechanical barrier comprises hydroxyethyl starch.

36. The composition according to claim 34, wherein the absorbable mechanical barrier comprises oxidized regenerated cellulose.

INTERNATIONAL SEARCH REPORT

Int. .onal Application No
PCT/US 96/08216

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/415 A61K31/05 A61K31/557 A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	INT. ARCH. ALLERGY APPL. IMMUNOL., vol. 78, no. 4, 1985, pages 429-437, XP000601219 D. FRICKE ET AL.: "Adhesion of guinea pig polymorphonuclear leukocytes to autologous aortic strips: influence of chemotactic factors and of pharmacological agents which affect arachidonic acid metabolism." ---	
A	PROSTAGLANDINS LEUKOTRIENES MED., vol. 11, no. 1, 1983, pages 109-119, XP000601216 M.F. GIMENO ET AL.: "Lipoxygenase inhibitors alter aggregation and adhesiveness of human blood platelets from aspirin-treated patients." ---	

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 1996	0 3. 10. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Klaver, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 96/08216

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THORAX, vol. 50, no. 4, 1995, pages 415-421, XP000601085 S.H. PHAN : "New strategies for treatment of pulmonary fibrosis." ---	
A	WO,A,94 26249 (MARGOLIN) 24 November 1994 ---	
A	US,A,4 937 254 (SHEFFIELD ET AL.) 26 June 1990 -----	

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/US 96/08216

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9426249	24-11-94	AU-A-	6829194	12-12-94
		BR-A-	9406461	30-01-96
		CA-A-	2161648	24-11-94
		EP-A-	0702551	27-03-96
		NO-A-	954437	06-11-95
		US-A-	5518729	21-05-96
US-A-4937254	26-06-90	AU-B-	587299	10-08-89
		AU-A-	6570986	04-06-87
		DE-A-	3683606	05-03-92
		EP-A-	0225162	10-06-87
		JP-B-	7098755	25-10-95
		JP-A-	62155223	10-07-87
		KR-B-	9406321	16-07-94